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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/814,752

03/31/2004

Paul L. DeAngelis

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12/04/2008

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EXAMINER

HUTSON, RICHARD G

ART UNIT

PAPER NUMBER

1652

MAIL DATE

DELIVERY MODE

12/04/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,752	DEANGELIS, PAUL L.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 June 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8 and 19-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8 and 19-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/2008</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The examiner of your application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1652, Examiner Richard Hutson Ph.D.

Applicant's amendment of claim 8 and 19, in the paper filed on 6/24/2008, is acknowledged. Claims 8 and 19-23 are pending.

Applicants' arguments filed on 6/24/2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

Applicants submission of the reference AX on the information disclosure statement filed November 30, 2004 , is acknowledged and this single page has been considered, however, applicants description of the reference appears to be lacking and it is requested that applicants provide a complete citation of the reference information including: name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book magazine, journal, serial, symposium, catalog, etc~), date, page(s), volume-issue number(s), publisher, city and/or country where published .

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 8 and 19-23 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, based upon new matter is withdrawn based upon applicants arguments presented in the paper of 6/24/2008.

Claims 8 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection was stated in the previous office action as it applied to previous claims 8 and 19-23. In response to this rejection applicants have amended claims 8 and 19 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse the rejection on the basis that they have cancelled items (E) and (F) in independent claims 8 and 19 and thus request the withdrawal of this rejection.

Applicants amendment and complete argument is acknowledged and has been carefully considered, however is found nonpersuasive on the basis that while applicants have cancelled items (E) and (F) of applicants claims, the scope of the items in (C) and (D) continue to overlap the same subject matter that was previously stated as not being described. As previously stated, since the recited items of the claim continue to encompass fragments can be of any size and is not limited to having heparin synthase activity, the claims encompass the genus of heparin synthases both naturally occurring and man made having any structure and properties defined by enzymatic function only.

It continues that the specification fails to describe any other representative species from any source by any identifying characteristics or properties other than the functionality of being heparin synthase and does not disclose the structure: function correlation common to all members of the genus. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 8 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a heparin polymer from UDP-GlcNAc and UDP-GlcUA using heparin synthase of SEQ ID NOs:2, 13 or 15 in the presence of divalent ion and a method elongating the acceptor using the same, does not reasonably provide enablement for methods of use of heparin synthase having an amino acid sequence with a mere 70% identity to SEQ ID NOs: 13 or 15 or encoded by a DNA that hybridizes to SEQ ID NOs: 12 or 14 under hybridization conditions recited in clause “(D)” of claims 8 and 19 as well as for a method for elongating the acceptor without a divalent ion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make the invention commensurate in scope with these claims.

This rejection was stated in the previous office action as it applied to previous claims 8 and 19-23. In response to this rejection applicants have amended claims 8 and 19 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse the rejection on the basis that Applicant clearly demonstrates production of four full-length heparin/heparosan synthases (two pmHS1 with GenBank Accession Nos. AF425591 and AF439804, and two pmHS2 with GenBank Accession Nos. AY292199 and AY292200), and three soluble heparin/heparosan synthases, pmHS1K45M-617, pmHS1177M-617, and thioredoxin fused wild type pmHS1. Applicants submit that the disclosure of these species constitutes adequate disclosure of a genus of heparin/heparosan synthases, and therefore Applicant should not be

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limited to the specific sequences disclosed therein but rather should be entitled to claims directed to the genus. Applicant has offered two ways that are typically acceptable to the Office for claiming such genus: the first method of claiming such genus is through the use of percent identity to the disclosed sequences; the second is through the use of hybridization language and specific hybridization conditions are included in the claims as a limitation.

Applicants submit that based on the disclosures of the present application the specification clearly establishes regions of the protein structure which may be modified without affecting heparin/heparosan synthase activity, as well as a rational and predictable scheme for modifying residues in heparin/heparosan synthases with an expectation of obtaining the desired biological function.

Applicant submits that the sequences and alignments disclosed in the subject application provide a person of ordinary skill in the art with the required reasonable amount of guidance to practice the presently claimed invention. While the Examiner has asserted there are "essentially infinitely possible choices", Applicant respectfully directs the Examiner's attention to *Ex parte Chen* (61 USPQ2nd (BNA) 1025, 2000 WL 33671755 (Bd. Pat. App & Interferences 2000), in which it was recognized that the success rate for practicing the invention taught therein was low, but in which the Board stated that "the numbers emphasized by the Examiner would reasonably appear to reflect the need for a repetitive procedure, rather than undue experimentation".

In support of the rejection, the Examiner cites *In re Wands* (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988)), which lays out factors to be considered in determining whether undue experimentation is required. However, Applicant would also like to direct the Examiner's attention to Page 1404 of *In re Wands*, where the court explained that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed". Applicant respectfully submits that the specification of the subject application provides such reasonable amount of guidance (as outlined above) to enable a person having ordinary skill in the art to identify nucleic acid segments, recombinant vectors and recombinant host cells that meet the limitations of the claims of the subject application.

In addition, Applicant has directed the Examiner's attention to several other patents that have issued in which Applicant is a co-inventor. Applicant submits that they are simply attempting to obtain similar patent protection for the heparin/heparosan synthase enzymes that he has identified, and respectfully submits that he is entitled to such patent protection.

Therefore, Applicant respectfully submits that the specification of the subject application fully enables the invention as claimed without requiring undue experimentation.

Applicants complete traversal is acknowledged and has been carefully considered, however, is found nonpersuasive for the reasons previously made of record and repeated herein.

Applicants disclosures of the present application and the specification with respect to the specifically recited protein and nucleic acid sequences as well as regions of the protein structure which may be modified without affecting heparin/heparosan synthase activity, as well as a rational and predictable scheme for modifying residues in heparin/heparosan synthases with an expectation of obtaining the desired biological function are acknowledged, however, such is insufficient to enable the breadth of the claimed genus of heparin/heparosan synthases.

While applicants disclose a few sequences and alignments, such is insufficient to provide a person of ordinary skill in the art with the required amount of guidance to practice the presently claimed invention. While the number of choices may not be "an infinite number of possible choices", it remains that such are too large to provide adequate enablement.

While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants useful as glucoamylases requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without sufficient guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the

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rejected claims would clearly constitute undue experimentation. Guo et al. (H. Guo et al., "Protein Tolerance to Random Amino Acid Change", PNAS 101(25): 9205-9210, June 2004) teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x \times 100\%$ where x is the number of mutations introduced. Applying this estimate to a protein of 80% identity to a full length protein, allows up to 118 mutations within a full length 591 amino acid protein and thus only $(.66)^{118} \times 100\%$ or $5.1 \times 10^{-20}\%$ of random mutants having 80% identity would be active. Similarly at 85% identity only $1.3 \times 10^{-14}\%$ would be active, at 90% identity, $3.4 \times 10^{-9}\%$ would be active and at 95% identity $5.8 \times 10^{-6}\%$. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand or up to about a million inactive mutants as is the case for the claims limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the claims to 90% or less identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification.

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Finally while applicants have referenced other patent applications in their argument, applicants are reminded that each patent application is an independent application and is given independent consideration.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including those methods of use of heparin synthase having an amino acid sequence with a mere 70% identity to SEQ ID NOs: 13 or 15 or encoded by a DNA that hybridizes to SEQ ID NOs: 12 or 14 under hybridization conditions recited in clause "(D)" of claims 8 and 19. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8 and 19-23 are rejected under 35 U.S.C. 102(b) as being anticipated by DeAngelis et al. (JBC, March 1, 2002, Vol. 277, pages 7209-7213, form PTO-1449 filed 11/30/04, reference CG).

This rejection was stated in the previous office action as it applied to previous claims 8 and 19-23. In response to this rejection applicants have amended claims 8 and 19 and traverse the rejection as it applies to the newly amended claims.

Applicants traverse the rejection on the basis that applicants submit that the presently disclosed and claimed invention is not directed to a full length heparin/heparosan synthase that is membrane-associated as is disclosed by DeAngelis et al. Rather, the presently disclosed and claimed invention relates to a **soluble** heparin/heparosan synthase. In contrast to the membrane-associated protein, soluble heparin/heparosan synthase is easy to purify, and the expression level thereof can be increased without overloading the membrane while still retaining enzymatic activity (see paragraph [0054]).

Applicants compete argument is acknowledged and has been carefully considered, however, is found non-persuasive for the reasons previously made of record and repeated herein.

As previously stated, DeAngelis et al. teach heparosan synthases from *Pasteurella multocida* and nucleic acids encoding them (GenBank accessions AF425591 and AF439804, page 7209). AF 425591 is 100% identical to SEQ ID NO: 1 and it encodes the amino acid sequence that is 100% identical to SEQ ID NO:2 of the

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instant invention. AF425591 encodes the sequence residues 46-617 differ from residues 2-573 of SEQ ID NO:13 by a single substitution (99.7% identical). AF439804 encodes the sequence that differs from SEQ ID NO:2 by a single substitution (99.8% identical). SEQ ID NO:13 is 99.8% identical to the amino acid sequence encoded by AF439804 with residues 2-573 of SEQ ID NO:13 being 100% identical to residues 46-617 of the DeAngelis sequence. Therefore, DeAngelis teach heparin synthases having at least 70% identical to SEQ ID NOs: 2, 13 and 15 that are encoded by a DNA that hybridizes to SEQ ID NOs: under low, medium and high stringency conditions or a DNA comprising a fragment of SEQ ID NOs: 1, 3, 12 or 14.

DeAngelis et al teach a method for producing a heparin polymer, i.e. the method of claim 8 (pages 7210-7211) and a method for producing a polymer by elongating the functional acceptor, i.e., the method of claims 19-23 (page 7211, Table 1, Figure 2). They teach that both methods must be carried out in the presence of the divalent ions (page 7211, 1st column).

NOTE: SEQ ID NOs: 1 and 2 are disclosed in provisional application 60/303,691 filed July 6, 2001, to which the parent application 10/142,143 filed May 8, 2002 claims priority, SEQ ID NO:3 is disclosed only in 10/142,143. However, SEQ ID NOs: 12-15 are disclosed neither in 10/142,143 nor in 60/458,939 filed March 31, 2003. Therefore, the effective filing date for the purposes of the prior art with regard to SEQ ID NOs: 12-15, is the filing date of 10/814,752, i.e. March 31, 2004.

Contrary to applicants traversal, the method taught by DeAngelis et al. does comprise "providing a soluble heparin/heparosan synthase...". Applicants submission

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that because the claimed invention is not directed to "full length heparin/heparosan synthase that is membrane associated" and DeAngelis et al. teach a full-length membrane associated heparosan synthase is not persuasive in traversal of the previous rejection.

The method taught by DeAngelis et al. comprises the transfection of bacterial cells with the plasmid pmHS-(1-617), followed by culturing, ultrasonication and assay of crude membrane preparations for activity. The taught method would inherently comprise providing a soluble heparin/heparosan synthase. Just because the DeAngelis et al. express the full-length heparin/heparosan synthase, does not mean that the expressed and tested heparin/heparosan synthase is not soluble. The method taught by DeAngelis et al. does comprise providing a soluble heparin/heparosan synthase.

While the office does not have the means to perform the methods taught by DeAngelis et al., the office relies upon that taught by DeAngelis et al. as well as the structural description of heparin/heparosan synthases recited by applicants in applicants claims. It is on this basis that the methods taught by applicants remain anticipated by DeAngelis et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rg
11/7/2008

/Richard G Hutson/
Primary Examiner, Art Unit 1652